CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

California Institute for Regenerative Medicine
Strategic Planning Advisory Committee Meeting
Scientific Strategic Planning
August 1, 2006

The fifth meeting of the Strategic Planning Advisory Committee (SPAC) included a progress report on interviews and meetings conducted to date as well as a discussion on the topic of clinical trials and CIRM's role in supporting them. In the course of this meeting, a number of ideas arose which are presented below. These notes are not intended to be comprehensive with respect to reporting these ideas; inclusion in these notes does not imply any commitment or endorsement by the CIRM. (Note: The questions discussed at this meeting were not necessarily discussed in the order in which they are presented in Section B2 below; questions and the related responses were grouped to allow for a better understanding of the issues that were addressed.)

A. Progress Report

1. Update on Interviews

a. The information gathering phase of the project is almost complete and the synthesis and analysis of that information has begun.
   i. To date, 59 interviews have been completed, 8 are scheduled, and 4 more are being scheduled. This will essentially complete the interviews.

2. Update on Meetings

a. The planned meetings are almost complete, with three having been held since the July 10 SPAC meeting:
   i. On July 13th, a scientific meeting was held to discuss the scientific challenges of advancing stem cell therapies from the bench to the bedside.
   ii. On July 25, a meeting was held with representatives from the private sector to discuss the challenges facing stem cell companies and how CIRM can work with industry to facilitate R&D for therapies and diagnostics in California.
   iii. On July 17th, a focus group meeting was held with 17 patient advocates. The meeting was organized by David Serrano Sewell and Susan DeLaurentis and moderated by Patricia Olson.
   iv. On August 1, there will be an official ICOC meeting to discuss values and the mission statement for the strategic plan.

b. In addition:
   i. There is an ICOC meeting scheduled for October 10-11.

ii. September 29th is the estimated date for completion of the draft of the strategic plan that will go to the ICOC for review.
iii. The next SPAC meetings are anticipated for August 24th and September 11th.

3. Update on the Strategic Planning Process

a. The first challenge in assembling the plan is how to organize all the information we have collected. A preliminary version of the strategic plan outline, which will be brought to the SPAC at the August 24th meeting, is being developed.
   i. The strategic planning team will organize the information that CIRM has received and while the specifics won't be in place by the 24th, the team will look for feedback from the SPAC on that day.
   ii. The expectation is that we will bring the outline back to the SPAC on September 11th and focus on areas where we may need additional advice.

b. The intent is to bring a draft of the scientific strategic plan to the ICOC in October and have a final plan in December.

c. The Governor has requested that the state make a $150 million loan to CIRM; funds will be available soon.
   i. This funding will allow CIRM to proceed with new initiatives earlier than anticipated. CIRM plans to propose to the ICOC tomorrow [August 2] an initiative which includes several components and focuses on human embryonic stem cells. Although the scientific strategic plan has not been completed, this initiative comprises an obvious, early element of our strategy. CIRM believes it can start sending out Requests for Application (RFAs) this month [August] for some parts of the initiative. CIRM is unlikely to pursue additional initiatives without a strategic plan in place.
   ii. Pending sufficient agreement on the plan in October or plan approval in December, CIRM will act expeditiously to implement the plan through additional funding initiatives by the first part of next year.

d. CIRM will ensure a careful, sound evaluation of all grant applications.
   i. Until the completion of the completion of the development and implementation of CIRM's web based grant management software, CIRM has a very labor-intensive review process for developing funding recommendations on grant applications for ICOC consideration.

B. Discussion Topic - Clinical Trials

1. Introduction

a. This topic originated from the scientific meeting in October 2005, when Dr. Rob Negrin from Stanford discussed some of the difficulties of doing clinical trials in the academic setting, and was also discussed during the conference on July 25th.
   i. Dr. Negrin's talk pointed out the need to do clinical research and the importance of doing it in an academic setting.
      - Trials should attempt to get mechanistic information to help determine if treatment is efficacious.

- There is much to be learned from negative as well as positive results from a well designed trial.
- Academic researchers are largely dependent on big pharma for financial support to carry out clinical trials.
- Clinical research has a regulatory and manpower burden (for example, getting approvals for trials to move forward, managing the data, managing the patients in the trial, etc.); all this requires financial support.

b. While CIRM may support clinical trials, we have been cautioned as to the expense involved. One interviewee in particular cautioned that the cost of clinical trials is "more than you can imagine" and that anyone trying to do clinical trials outside of pharma would find it very difficult.

c. One interesting model CIRM studied was the clinical trials network.
   i. CIRM could put together a clinical trials network with multiple centers to provide a framework to facilitate clinical trials.
   ii. One challenge for CIRM is that stem cells are applicable to many diseases, whereas most clinical trials networks are disease specific; CIRM is therefore not certain how many of such networks it is able to support.
   iii. The final consideration is that for many diseases, the patient population (or a large enough patient population) may not be in California. Proposition 71 limits financial support to inside the state. Also existing, successful networks may be nationwide rather than state-based.

2. Discussion Questions

a. Do you see a role for academic physician–initiated (sponsored) clinical research as well as industry initiated clinical research in a new therapeutic modality such as stem cell therapy?
   i. As there may be a role for both, CIRM might support investigator ideas and the development of preclinical data to take the proposed stem cell related therapy into trials and / or partner with a company that has a device / drug to be tested in a selected population.
   ii. CIRM should not close the door to either investigator-initiated research or industry-initiated research because good ideas may come from both.
   iii. Early stem cell trials may likely be investigator-initiated.

b. Where does the funding for academic physician–initiated (sponsored) clinical trials come from?
   i. Investigators write grants to support those trials, sometimes as part of R-01 or R-21 [types of NIH grants] application. These funds are often combined with institutional support and development funds.
   ii. There may be a general need for private philanthropy or other non-federal funds to support the use of non-presidential cells in clinical trials.

c. How do you take an idea and bring it to an industry sponsor?

i. When investigators have an idea that industry needs or that is truly novel, they contact industry. There are also mechanisms like CTEP [the National Cancer Institute's Cancer Therapy Evaluation Program] for certain drugs.

ii. Industry and investigators at academic medical centers may work jointly to design clinical trial protocols where the investigator has specialized expertise and/or access to the necessary patient population for the trial.

d. What useful role can CIRM play with respect to clinical trials? Should CIRM give out grants for clinical trials and issue a call for application? Should CIRM fund on a project-by-project basis or have some infrastructure in place (for example, to help with regulatory matters, which is labor-intensive and requires expertise)? How can CIRM support cell processing, which will be needed to scale up production of cells for clinical trials?

i. An important "sweet spot" for CIRM may be in facilitating translation from basic science into the clinic.

- There will always be some investigators who are not "ready for prime time"; a review committee can play an important role in critiquing the investigators.

ii. The Center for Human Cell Therapy (CHCT) receives internal grant applications that involve work at the preclinical stage that could benefit from cGMP cell production. CHCT provides grants and space as well as regulatory and technical support to get these cells produced and tested in preclinical models. CHCT is funded by NIH 'block' grants and has a steering committee which decides which projects to fund. There are 4 slots per year with generally 10-12 applicants. Post meeting information: The CHCT was created by the CBR Institute for BioMedical Research, a non-profit independent research organization affiliated with Harvard Medical School. The mandate of the CHCT is to provide resources to all Harvard Medical School faculty to facilitate bench-to-bedside development of cellular therapies for the treatment of damaged or diseased tissues. It does this through providing a translational infrastructure including the Translational Cell Therapy Laboratory, a regulatory core and a flow cytometry core.

iii. Investigator-initiated trials with stem cells are unlikely to attract commercial interest in the near-term given the challenges of cell therapy and the newness of stem cell therapies.

iv. CIRM may therefore also have a role in providing support from the pre-clinical stage through Phase I and even Phase II trials not only for investigator-initiated studies in academic medical center but also to companies. Companies, especially smaller companies, may find it difficult to get funding from conventional sources for stem cell therapies.

v. There was some debate about releasing an RFA for clinical trials.

- It was suggested that, assuming the strategic plan makes it clear that CIRM will support clinical trials as a priority, there may not be a need for RFAs to determine types of clinical trial on which to focus; the applications may come on their own.
- There was the suggestion that, at this time, a RFA for funding of clinical trials of stem cell related therapies would be premature. At this time,

there are unlikely to be many applicants who could demonstrate feasibility (e.g. cGMP production) to carry out trials using embryonic stem cell or most other types of stem cell products.

- That said, there is still a need to address what type(s) of mechanism(s) CIRM will use to solicit application for funding for clinical trials.

e. What specific services or networks might CIRM establish to facilitate stem cell-based clinical investigation that would be of value to physician-initiated and / or industry-initiated clinical research?

i. As stem cells can target a variety of diseases, it might be challenging to establish disease-specific networks. A broader based approach, such as a network that provides some type of clinical assay service, may be of interest.

ii. As the trials CIRM may support are likely to be Phase 0 [which are not currently available through the FDA Center for Biologics Evaluation & Research, the regulatory authority for cell therapies] and Phase I trials, which do not require large numbers of patients, CIRM's efforts may not be network driven.

iii. It will be critical for CIRM to facilitate strategic thinking about clinical research/development.

- For example, preclinical data needs to be collected such that it informs the clinical plan; CIRM should think about how best to support efforts in strategic clinical thinking to provide safety and efficacy information for stem cell therapies.
- Setting up potential trainee or mentor relationships or collaborations with persons experienced in clinical development could address the above.
- Similarly, CIRM should also think strategically about providing support to help investigators deal with regulatory issues.

iv. In the future, CIRM can also host a clinical trial symposium to attract people interested in stem cell-based clinical research.

f. Are there things CIRM can do in training (i.e., in clinical trial design)?

i. Clinical and translational fellowships might be one approach.

ii. A resource that could help "amateurs" vet the data they have to determine if they are ready to go into clinical trial could also be valuable.

iii. Some institutions (such as NIH-designated Comprehensive Cancer Center) employ a review committee, in addition to an IRB, that looked at clinical trial design, including the statistical analysis plan.

- This can improved the quality of the studies but may build an inherent delay into the approval process.
- Also, some institutions experience a "wide gamut of quality" with respect to these reviews.

iv. With respect to the clinical trials CIRM plans to support, if they are done under an Investigational New Drug application (IND), the regulatory oversight and reporting requirements will likely be intense, though it may be possible to do the work without an IND.

- The regulatory review process for investigator-initiated trials used to be less rigorous, but these trials would now likely face the same level of regulatory rigor as in an industry-sponsored study.

g. In terms of oversight, would CIRM need to provide for a data safety monitoring board (DSMB)?

i. It is often the responsibility of the author of the proposal to outline how safety monitoring would be handled.
ii. A DSMB is often needed in the case of blinded trials where there is interim analysis involved. At some institutions, the IRB essentially serves the role as the safety monitor.
iii. Some institutions use both approaches, with the IRB and DSMB reviewing some protocols and the IRB alone reviewing others.

h. How should CIRM work within Proposition 71 to review the large number of grants we want to review? Is there a need to have a dedicated group or someone with a high level of expertise in a given area (for example, clinical trials, ethical issues) in the Grants Working Group (GWG)? Does CIRM need different committees for different kinds of grants?

i. There might be a possibility of using a standing group to provide oversight.
ii. As some people on the GWG might not be experts in the area of private sector grants or pre-clinical research, this is a challenge CIRM needs to work out.
iii. The Standards Working Group (SWG) has members with clinical experience and might be a short-term solution.
iv. As "clinical readiness" of stem cell therapies becomes apparent, CIRM would require a special committee with relevant therapy development expertise to review applications for a variety of trials among the spectrum of disorders.

i. How can the use of non-approved lines go on within a facility without coming too close to the line we are trying to stay away from (that is, making sure federal funding is not used on non-approved lines)?

i. Possibilities might include a private arrangement or going to the private sector.
ii. There may be benefit in CIRM having any cell production facilities it might support free and clear of these concerns and uncomplicated by federal factors, particularly if CIRM focuses on non-approved lines.
iii. The GMP facility at Harvard is partly NIH funded but has administrative policies and financial accounting processes in place which allows the separation of presidential and non-presidential stem cell work.

j. Are the hospital facilities where the patients in clinical trials would be maintained partially paid for by NIH funds? If so, would that be an additional barrier to the use of non-approved lines to conduct clinical trials?

i. There are NIH-funded clinical research centers and a very few places where every bed is constrained in this way. Such constraints are unlikely to have a negative impact on clinical research involving stem cells as long as the institution doing the clinical research is able to keep federal and non federal-funded research separate.

ii. While General Clinical Research Centers (GCRCs) must follow NIH guidelines for stem cell research, not all procedures involving stem cells would be in-patient procedures.

iii. Allocating space in a basic laboratory involves a process similar to allocating overhead in the clinical setting. CIRM might speak with the finance offices at UCSF or Stanford, which seem comfortable with these issues.

k. Will there be any problems for stem cell line-derived therapies with respect to regulatory consideration?

i. The FDA focuses on the safety and efficacy of therapies; whether or not these therapies use presidential or and non-presidential lines may not be an issue.

ii. At the same time, CIRM continues to be aware of potential issues related to the use of non-presidential lines for therapies.

l. What role should CIRM play in supporting effort to educate both the patient and physician community about the benefits and risks of clinical trials related to stem cell based or derived therapies?

i. The July 13th Scientific Conference touched on the need to involve patient advocates as part of clinical trial process. As it can often be miscommunication that leads to negative outcomes, CIRM should have clinical trial networks and patient advocacy groups involved early on.

ii. Audience members added that CIRM "must not say anything that hasn't been thought out carefully first", "should be careful in dealing with the flicker of hope, because rushing into anything can be harmful", and "should be realistic about creating the 'right amount' of hope".

iii. There is a need for careful education on the nature and the reality of clinical trials. CIRM has to help the public understand the expectations, obstacles, risks, and limitations for clinical trial; this is a long-term process.

iv. To date, public education has been fairly effective in California and CIRM should support these efforts. At the same time, CIRM should anticipate its response the first serious adverse event.

v. As large parts of the population of California use the internet, this may be a vehicle CIRM can utilize to create its own educational network.

vi. Concern about the use of non-presidential stem cells for clinical trials might not be an issue for the public for some time.